PALM INTRANET

Day : Sunday
Date: 9/1/2002
Time: 15:46:00

Inventor Name Search

Enter the **first few letters** of the Inventor's Last Name.
Additionally, enter the **first few letters** of the Inventor's First name.

Last Name	First Name	
kranz	david	Search

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Day : Sunday
Date: 9/1/2002
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Inventor Name Search

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Last Name	First Name	
holler	phillip	Search

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? set hi ;set hi
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      Set  Items  Description
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? s T (n) cell (n) receptor? or TCR?
Processing
Processing
Processed  10 of  37 files ...
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Processed  20 of  37 files ...
Completed processing all files
         9257697  T
        13775514  CELL
         5019402  RECEPTOR?
          172424  T(N)CELL(N)RECEPTOR?
          134010  TCR?
      S1  228909  T (N) CELL (N) RECEPTOR? OR TCR?
? s s1 and soluble and CDR3?
          228909  S1
          970967  SOLUBLE
           11554  CDR3?
      S2     102  S1 AND SOLUBLE AND CDR3?
? s s2 and mutate?
             102  S2
          156707  MUTATE?
      S3       8  S2 AND MUTATE?
? rd s3
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      S4       2  RD S3 (unique items)
? d s4/3/1-2
      Display 4/3/1     (Item 1 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

13446224   22103697   PMID: 12093915
   Cytotoxic  T lymphocytes directed against a tumor-specific mutated
antigen  display  similar  HLA  tetramer  binding  but  distinct functional
avidity and tissue distribution.
  Echchakir  Hamid;  Dorothee  Guillaume;  Vergnon  Isabelle; Menez Jeanne;
Chouaib Salem; Mami-Chouaib Fathia
  Laboratoire  Cytokines et Immunologie des Tumeurs Humaines, U487 Institut
National  de la Sante et de la Recherche Medicale, Institut Gustave Roussy,
Institut Federatif de Recherche-54, F-94805 Villejuif, Cedex, France.
  Proceedings  of  the National Academy of Sciences of the United States of
America (United States)   Jul 9 2002,  99  (14)  p9358-63,  ISSN 0027-8424
Journal Code: 7505876
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed

                                - end of record -
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      Display 4/3/2     (Item 2 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

10507352   20040405   PMID: 10570300
  Selection  of  CTL  escape  mutants  in  mice infected with a neurotropic
coronavirus:  quantitative  estimate of TCR diversity in the infected
central nervous system.
  Pewe L; Heard S B; Bergmann C; Dailey M O; Perlman S
  Departments   ofPediatrics,   Biological   Sciences,   Pathology,   and
Microbiology and the Interdisciplinary Program in Immunology, University of
Iowa, Iowa City, IA 52242, USA.
```

Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Dec 1 1999, 163 (11) p6106-13, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: AI22730; AI; NIAID; AI43497; AI; NIAID; NS36592; NS; NINDS; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

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>>>Page beyond end of display invalid
? rd s2
...examined 50 records (50)
>>>Record 266:203304 ignored; incomplete bibliographic data, not retained - in RD set
...examined 50 records (100)
...completed examining records
S5 34 RD S2 (unique items)
? d s5/3/1-34
Display 5/3/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13591537 BIOSIS NO.: 200200220358
Unexpected T cell diversity in syngeneic graft-vs-host disease revealed by interaction with peptide-loaded **soluble** MHC class II.
AUTHOR: Chen Weiran(a); Thoburn Chrostopher(a); Bright Emily(a); Hess Allan (a)
AUTHOR ADDRESS: (a)Oncology, Johns Hopkins University, Baltimore, MD**USA
JOURNAL: Blood 98 (11 Part 1):p653a November 16, 2001
MEDIUM: print
CONFERENCE/MEETING: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English

- end of record -

?
Display 5/3/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12675291 BIOSIS NO.: 200000428793
Functional characterization of an IL-7-dependent CD4+CD8alphaalpha+ Th3-type malignant cell line derived from a patient with a cutaneous T-cell lymphoma.
AUTHOR: Poszepczynska Eva; Bagot Martine; Echchakir Hamid; Martinvalet Denis; Ramez Mohamed; Charue Dominique; Boumsell Laurence; Bensussan Armand(a)
AUTHOR ADDRESS: (a)INSERM 448, Faculte de Medecine de Creteil, 8 rue, du General Sarrail, 94010, Creteil**France
JOURNAL: Blood 96 (3):p1056-1063 August 1, 2000
MEDIUM: print
ISSN: 0006-4971
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

- end of record -

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Display 5/3/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12513659 BIOSIS NO.: 200000267161
In vitro evolution of a **T cell receptor** with high affinity for peptide/MHC.
AUTHOR: Holler Phillip D; Holman Philmore O; Shusta Eric V; O'Herrin Sean; Wittrup K Dane; Kranz David M(a)
AUTHOR ADDRESS: (a)Department of Biochemistry, University of Illinois, Urbana, IL, 61801**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 97 (10):p5387-5392 May 9, 2000
MEDIUM: print.
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

- end of record -

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Display 5/3/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12210815 BIOSIS NO.: 199900505664
Involvement of **soluble** CD95 in Churg-Strauss Syndrome.
AUTHOR: Mueschen Markus; Warskulat Ulrich(a); Perniok Andreas; Even Jos; Moers Cordula; Kismet Berrin; Temizkan Nazan; Simon Dietmar; Schneider Matthias; Haeussinger Dieter
AUTHOR ADDRESS: (a)Medizinische Universitaetsklinik, Heinrich-Heine Universitaet Duesseldorf, Moorenstrasse 5, D-40225, Duesseldorf**Germany
JOURNAL: American Journal of Pathology 155 (3):p915-925 Sept., 1999
ISSN: 0002-9440
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

- end of record -

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Display 5/3/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12084825 BIOSIS NO.: 199900379674
In vitro expansion of **T-cell-receptor** Valpha2.3+ CD4+ T

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? s s1 and dissociation (n) constant
          228909  S1
          472213  DISSOCIATION
         1843576  CONSTANT
           70473  DISSOCIATION(N)CONSTANT
      S6      99  S1 AND DISSOCIATION (N) CONSTANT
? rd s6
...examined 50 records  (50)
...completed examining records
      S7      50  RD S6 (unique items)
? d s7/3/1-50
      Display 7/3/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

13092104   BIOSIS NO.: 200100299253
Expression, characterization, and potential application of soluble
  recombinant proteins consisting of the extracellular domains of the CD3
  chains.
AUTHOR: Dua R(a); McNeill L(a); Thorne B(a); Nguyen H(a); Habecker P(a);
  Murali R; Greene M; Ledbetter J(a); Berenson R(a); Law C-L(a)
AUTHOR ADDRESS: (a)Xcyte Therapies, Inc., Seattle, WA**USA
JOURNAL: Blood  96 (11 Part 2):p153b November 16, 2000
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of
Hematology  San Francisco, California, USA  December 01-05, 2000
SPONSOR: American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English
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? s s6 and mutat?
99 S6
1987601 MUTAT?
S8 8 S6 AND MUTAT?
? d s8/3/1-8
Display 8/3/1 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

131098500 CA: 131(8)98500j PATENT
Yeast cell surface display of proteins and selection using FACS
INVENTOR(AUTHOR): Wittrup, K. Dane; Kieke, Michele C.; Kranz, David M.; Shusta, Eric; Boder, Eric T.
LOCATION: USA
ASSIGNEE: The Board of Trustees of the University of Illinois
PATENT: PCT International ; WO 9936569 A1 DATE: 19990722
APPLICATION: WO 99US1188 (19990120) *US 9388 (19980120) *US 140084 (19980826)
PAGES: 117 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12Q-001/02A; C12Q-001/68B; C12N-001/19B; C12N-015/63B; C12N-015/81B
DESIGNATED COUNTRIES: AU; CA; JP DESIGNATED REGIONAL: AT; BE; CH; CY; DE ; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE

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Display 8/3/2 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07223564 EMBASE No: 1998103207
A **mutational** analysis of the binding of staphylococcal enterotoxins B and C3 to the **T cell receptor** beta chain and major histocompatibility complex class II
Leder L.; Llera A.; Lavoie P.M.; Lebedeva M.I.; Li H.; Sekaly R.-P.; Bohach G.A.; Gahr P.J.; Schlievert P.M.; Karjalainen K.; Mariuzza R.A.
Dr. R.A. Mariuzza, Ctr. for Advanced Res. Biotechnol., Univ. of Maryland Biotechnol. Inst., 9600 Gudelsky Dr., Rockville, MD 20850 United States
AUTHOR EMAIL: mariuzza@indigo2.carb.nist.gov
Journal of Experimental Medicine (J. EXP. MED.) (United States) 16 MAR 1998, 187/6 (823-833)
CODEN: JEMEA ISSN: 0022-1007
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 37

- end of record -

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Display 8/3/3 (Item 1 from file: 370)
DIALOG(R)File 370:Science

00508924 (USE 9 FOR FULLTEXT)
Crystallographic Evidence for Preformed Dimers of Erythropoietin Receptor Before Ligand Activation
Livnah, Oded; Stura, Enrico A.; Middleton, Steven A.; Johnson, Dana L.; Jolliffe, Linda K.<CRF RID="C1"> ; Wilson, Ian A.<CRF RID="C1">
Department of Molecular Biology and Skaggs Institute of Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road., La Jolla, CA 92037, USA. R. W. Johnson Pharmaceutical Research Institute, Drug Discovery Research, 1000 Route 202, Box 300, Raritan, NJ 08869, USA.
Science Vol. 283 5404 pp. 987

Publication Date: 2-12-1999 (990212) Publication Year: 1999
Document Type: Journal ISSN: 0036-8075
Language: English
Section Heading: REPORTS
Word Count: 2223

- end of record -

?
Display 8/3/4 (Item 2 from file: 370)
DIALOG(R)File 370:Science

00505223 (USE 9 FOR FULLTEXT)
Structural Basis of Plasticity in **T Cell Receptor** Recognition of a Self Peptide-MHC Antigen
Garcia, K. Christopher; Degano, Massimo; Pease, Larry R.; Huang, Mingdong; Peterson, Per A.; Teyton, Luc; Wilson, Ian A.
K. C. Garcia, M. Degano, M. Huang, and I. A. Wilson are in the Department of Molecular Biology and the Skaggs Institute of Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA. L. R. Pease is in the Department of Immunology, Mayo Clinic, Rochester, MN 55905, USA. P. A. Peterson is at the R. W. Johnson Pharmaceutical Research Institute-La Jolla, 3535 General Atomic Court, San Diego, CA 92121, USA. L. Teyton is in the Department of Immunology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA.
Science Vol. 279 5354 pp. 1166
Publication Date: 2-20-1998 (980220) Publication Year: 1998

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Display 8/3/4 (Item 2 from file: 370)
DIALOG(R)File 370:Science

Document Type: Journal ISSN: 0036-8075
Language: English
Section Heading: Research Articles
Word Count: 5152

- end of record -

?
Display 8/3/5 (Item 3 from file: 370)
DIALOG(R)File 370:Science

00504965 (USE 9 FOR FULLTEXT)
Role of Substrates and Products of PI 3-kinase in Regulating Activation of Rac-Related Guanosine Triphosphatases by Vav
Han, Jaewon; Luby-Phelps, Katherine; Das, Balaka; Shu, Xiaodong; Xia, Yi; Mosteller, Raymond D.; Krishna, U. Murali; Falck, John R.; White, Michael A.; Broek, Daniel
J. Han, B. Das, X. Shu, Y. Xia, R. D. Mosteller, D. Broek, Department of Biochemistry and Molecular Biology, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA 90033-0800, USA. ; K. Luby-Phelps and M. A. White, Department of Cell Biology and Neuroscience, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75235-9039, USA. ; U. M. Krishna and J. R. Falck, Department of Biochemistry, University of Texas Southwestern Medical Center, ; 5323 Harry Hines Boulevard, Dallas, TX 75235-9039, USA.
Science Vol. 279 5350 pp. 558
Publication Date: 1-23-1998 (980123) Publication Year: 1998

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Display 8/3/5 (Item 3 from file: 370)
DIALOG(R)File 370:Science

Document Type: Journal ISSN: 0036-8075
Language: English
Section Heading: Reports
Word Count: 1766

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Display 8/3/6 (Item 4 from file: 370)
DIALOG(R)File 370:Science

00501436 (USE 9 FOR FULLTEXT)
Structural Insights into the Evolution of an Antibody Combining Site
Wedemayer, Gary J.; Patten, Phillip A.; Wang, Leo H.; Schultz, Peter G.; Stevens, Raymond C.
The authors are in the Department of Chemistry, University of California, Berkeley, CA 94720, USA and at the Lawrence Livermore National Laboratory, Berkeley; P. G. Schultz is also with the Howard Hughes Medical Institute.
Science Vol. 276 5319 pp. 1665
Publication Date: 6-13-1997 (970613) Publication Year: 1997
Document Type: Journal ISSN: 0036-8075
Language: English
Section Heading: Research Articles
Word Count: 4599

- end of record -

?
Display 8/3/7 (Item 5 from file: 370)
DIALOG(R)File 370:Science

00500521 (USE 9 FOR FULLTEXT)
Structure of the FKBP12-Rapamycin Complex Interacting with the Binding Domain of Human FRAP
Choi, Jungwon; Chen, Jie; Schreiber, Stuart L.; Clardy, Jon
J. Choi and J. Clardy, Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, NY 14853-1301, USA. ; J. Chen and S. L. Schreiber, Howard Hughes Medical Institute and Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA 02138, USA.
Science Vol. 273 5272 pp. 239
Publication Date: 7-12-1996 (960712) Publication Year: 1996
Document Type: Journal ISSN: 0036-8075
Language: English
Section Heading: Reports
Word Count: 2245

- end of record -

?
Display 8/3/8 (Item 6 from file: 370)
DIALOG(R)File 370:Science

00500143 (USE 9 FOR FULLTEXT)
The Immunological Evolution of Catalysis
Patten, Phillip A.; Gray, Nathanael S.; Yang, Priscilla L.; Marks, Cara B.; Wedemayer, Gary J.; Boniface, J. Jay; Stevens, Raymond C.; Schultz, Peter G.
P. A. Patten, N. S. Gray, P. L. Yang, and P. G. Schultz are in the Howard

Hughes Medical Institute, Department of Chemistry, University of California, Berkeley, CA 94720, USA. C. B. Marks, G. J. Wedemayer, and R. C. Stevens are in the Department of Chemistry, University of California, Berkeley, CA 94720, USA. J. J. Boniface is in the Howard Hughes Medical Institute, Department of Microbiology and Immunology, Stanford University, Stanford, CA 94305, USA.
Science Vol. 271 5252 pp. 1086
Publication Date: 2-23-1996 (960223) Publication Year: 1996
Document Type: Journal ISSN: 0036-8075
Language: English

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DIALOG(R)File 370:Science

Section Heading: Research Articles
Word Count: 4795

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DIALOG(R)File 370:Science

00500143 (THIS IS THE FULLTEXT)
The Immunological Evolution of Catalysis
Patten, Phillip A.; Gray, Nathanael S.; Yang, Priscilla L.; Marks, Cara B.; Wedemayer, Gary J.; Boniface, J. Jay; Stevens, Raymond C.; Schultz, Peter G.
P. A. Patten, N. S. Gray, P. L. Yang, and P. G. Schultz are in the Howard Hughes Medical Institute, Department of Chemistry, University of California, Berkeley, CA 94720, USA. C. B. Marks, G. J. Wedemayer, and R. C. Stevens are in the Department of Chemistry, University of California, Berkeley, CA 94720, USA. J. J. Boniface is in the Howard Hughes Medical Institute, Department of Microbiology and Immunology, Stanford University, Stanford, CA 94305, USA.
Science Vol. 271 5252 pp. 1086
Publication Date: 2-23-1996 (960223) Publication Year: 1996
Document Type: Journal ISSN: 0036-8075
Language: English

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Display 8/9/8 (Item 6 from file: 370)
DIALOG(R)File 370:Science

Section Heading: Research Articles
Word Count: 4795

Abstract: The germline genes used by the mouse to generate the esterolytic antibody 48G7 were cloned and expressed in an effort to increase our understanding of the detailed molecular mechanisms by which the immune system evolves catalytic function. The nine replacement **mutations** that were fixed during affinity maturation increased affinity for the transition state analogue by a factor of 10.sup(4), primarily the result of a decrease in the dissociation rate of the hapten-antibody complex. There was a corresponding increase in the rate of reaction of antibody with substrate, k.inf(cat)/K.inf(m), from 1.7 x 10.sup(2) M.sup(-1) min.sup(-1) to 1.4 x 10.sup(4) M.sup(-1) min.sup(-1). The three-dimensional crystal structure of the 48G7-transition state

analogue complex at 2.0 angstroms resolution indicates that none of the nine residues in which somatic **mutations** have been fixed directly contact the hapten. Thus, in the case of 48G7, affinity maturation appears

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Display 8/9/8 (Item 6 from file: 370)
DIALOG(R)File 370:Science
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to play a conformational role, either in reorganizing the active site geometry or limiting side-chain and backbone flexibility of the germline antibody. The crystal structure and analysis of somatic and directed active site mutants underscore the role of transition state stabilization in the evolution of this catalytic antibody

Text: The immune response provides a means to rapidly generate high affinity, selective receptors for an enormous array of chemical structures. The primary immune response occurs through the generation and screening of a large and diverse library of antibody combining sites, resulting from the combinatorial rearrangement of variable (V), diversity (D), and joining (J) gene segments (B1) . Antigen-antibody recognition is optimized during the secondary and tertiary responses through the somatic hypermutation of antibody genes (B2) in clonally expanding populations of B cells, with concomitant selection between competing clones for increasingly rare antigen (B3) . This process results in a population of rapidly evolving B cells that produce antibodies of increasing affinity as the immune response

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DIALOG(R)File 370:Science
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proceeds, giving rise to the well-known phenomenon of affinity maturation (B4) (B5) .

There are parallels between this process and the natural evolution of enzyme active sites. The latter also arise by a process involving the generation of molecular diversity, in this case by exon shuffling and point **mutations** (B6) , coupled with a selection generally based on catalytic efficiency. Whereas antibodies are selected on the basis of affinity for stable antigens, enzymes evolve based on catalytic efficiency which in turn is correlated with affinity for high energy, transition states (B7) (B8) . The similarities between natural selection and the immune response suggest that, with proper chemical instruction, the latter can be directed along the same pathway as enzymatic evolution to afford catalytic antibodies. Indeed, when stable transition state analogues are used as immunogens, antibodies can be generated that catalyze a large number of different reactions, from disfavored cyclization reactions to pericyclic and redox reactions (B9) (B10) . In some cases, the rates of the antibody-catalyzed reactions approach those of comparable enzyme-catalyzed

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reactions (B11) , and in others, antibodies have been generated that catalyze reactions for which there is no known enzymic counterpart (B12) .

In order to reconstruct the immunological evolution of a catalytic antibody, we cloned the germline genes of the esterolytic antibody 48G7. Expression of the corresponding antibody (B13) (B14) allowed us to reconstruct the immunological evolution of this catalytic antibody by characterizing the functional consequences of affinity maturation on hapten binding and catalysis. In addition, the three-dimensional x-ray crystal

structure of the Fab fragment of 48G7, complexed with the transition state analogue against which it was elicited, was solved at 2.0 angstrom resolution. This structure, along with a mutagenesis study of active site residues, has provided insight into the mechanism of this antibody-catalyzed reaction. The crystal structure has also made it possible to begin to interpret the effects of somatic **mutation** in structural and functional terms.

Functional characterization of the germline antibody. Antibody 48G7, which binds the p-nitrophenyl phosphonate transition state analogue 3,

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DIALOG(R)File 370:Science
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catalyzes the hydrolysis of the corresponding p-nitrophenyl ester 1 and carbonate 2 with rate accelerations of 1.6 x 10.sup(4) and 4 x 10.sup(4), respectively, compared to the rates of uncatalyzed reaction (B14) . The antibody-catalyzed reaction is first order in hydroxide ion from pH 6.2 to 9.2 for substrate 2, and chemical modification studies suggested that arginine, tyrosine, and histidine residues are important in catalysis (B14) . In addition, 48G7 has been cloned (B13) and expressed in bacteria by fusing the V.inf(H) (heavy) and V.inf(L) (light) variable region genes to human C.inf(H)1 and C.inf((kappa)) constant regions, respectively (B15) (B16) . The values of the catalytic constant, k.inf(cat), and Michaelis constant, K.inf(m), of the purified chimeric Fab fragment for hydrolysis of ester 1 are 5.5 min.sup(-1) and 391 (mu) M, respectively, comparable to those for the hybridoma-derived antibody (k.inf(cat) = 2.1 min.sup(-1); K.inf(m) = 113 (mu) M) (B14) .

To determine the degree to which the binding and catalytic properties of 48G7 preexisted in the germline antibody, or evolved as a consequence of affinity maturation, the germline light (L) and heavy chain (H) variable

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region genes were cloned and sequenced. Nine replacement **mutations**, three in the light chain and six in the heavy chain, were fixed during the affinity maturation process (Fig. 1). The germline variable region genes were then combined with their respective D and J region sequences; the resulting Fab fragment was expressed in Escherichia coli, and its binding and catalytic properties were characterized (B15) (B16) . In addition, each of the reconstructed heavy and light chain germline genes (G.sup(H) and G.sup(L)) were expressed in combination with the partner from 48G7 to yield G.sup(H)48G7.sup(L) and G.sup(L)48G7.sup(HA functional analysis of these somatic **mutations** revealed that both hapten binding and catalytic activity increased during affinity maturation. The **dissociation constant** (K.inf(d)) of the germline Fab (mid-dot) 3 complex is 135 (mu) M compared to that of 10 nM for the 48G7 Fab (mid-dot) 3 complex, representing a 1.4 x 10.sup(4) improvement in binding affinity during the affinity maturation process (Table 1). The half-germline Fabs G.sup(L)48G7.sup(H) and 48G7.sup(L)G.sup(H) have intermediate K.inf(d)'s of 330 nM and 1860 nM, respectively. Paralleling this improvement in affinity,

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the k.inf(cat)/K.inf(m) value for substrate 1 (the bimolecular rate constant for reaction of free antibody with substrate) increased from 1.7

x 10.sup(2) M.sup(-1) min.sup(-1) for germline Fab to 1.4 x 10.sup(4) M.sup(-1) min.sup(-1) for 48G7. The low level of germline catalytic activity precluded measurement of k.inf(cat) and K.inf(m) independently. The increase in k.inf(cat)/K.inf(m) with increasing affinity for the transition state analogue is consistent with the concepts of enzymatic catalysis put forth by Pauling (B7) and Haldane (B8) in which preferential binding energy for the transition state lowers the activation energy for reaction of enzyme with substrate. Other factors (for example, binding of substrate and product and the environment around the attacking water molecule) that are less subject to selective pressure during the immune response may account for the imperfect correlation between binding affinity and catalytic efficiency. In fact, affinity maturation does lead to a moderate increase in affinity for the reaction product [K.inf(i) = 35 (mu) M (B14)] relative to the germline Fab (K.inf(d) > 200 (mu) M). This leads to increased product inhibition and is reflected in nonlinear

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Display 8/9/3 (Item 1 from file: 370)
DIALOG(R)File 370:Science

00508924 (THIS IS THE FULLTEXT)
Crystallographic Evidence for Preformed Dimers of Erythropoietin Receptor Before Ligand Activation
Livnah, Oded; Stura, Enrico A.; Middleton, Steven A.; Johnson, Dana L.; Jolliffe, Linda K.<CRF RID="C1"> ; Wilson, Ian A.<CRF RID="C1">
Department of Molecular Biology and Skaggs Institute of Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road., La Jolla, CA 92037, USA. R. W. Johnson Pharmaceutical Research Institute, Drug Discovery Research, 1000 Route 202, Box 300, Raritan, NJ 08869, USA.
Science Vol. 283 5404 pp. 987
Publication Date: 2-12-1999 (990212) Publication Year: 1999
Document Type: Journal ISSN: 0036-8075
Language: English
Section Heading: REPORTS
Word Count: 2223

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Abstract: Erythropoietin receptor (EPOR) is thought to be activated by ligand-induced homodimerization. However, structures of agonist and antagonist peptide complexes of EPOR, as well as an EPO-EPOR complex, have shown that the actual dimer configuration is critical for the biological response and signal efficiency. The crystal structure of the extracellular domain of EPOR in its unliganded form at 2.4 angstrom resolution has revealed a dimer in which the individual membrane-spanning and intracellular domains would be too far apart to permit phosphorylation by JAK2. This unliganded EPOR dimer is formed from self-association of the same key binding site residues that interact with EPO-mimetic peptide and EPO ligands. This model for a preformed dimer on the cell surface provides insights into the organization, activation, and plasticity of recognition of hematopoietic cell surface receptors.

Text: Erythropoietin (EPO) is a glycoprotein hormone that regulates the proliferation, differentiation, and maturation of erythroid cells (B1) .

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The EPO receptor (EPOR), a member of the class 1 cytokine receptor superfamily (B2) , consists of an extracellular ligand-binding domain, a short single-pass transmembrane segment, and a cytoplasmic domain that lacks a kinase region (B3) . Signaling occurs through the JAK/STAT pathway, where ligand-induced sequential receptor homodimerization (B4) (B5) (B6) has been proposed to promote stable association of JAK2 and phosphorylation of JAK2, EPOR, and STAT5 (B7) . EPOR can also be activated through a point **mutation** in the extracellular region (EPO binding protein, EBP) that produces a disulfide-linked homodimer (B5) , by a small percentage of monoclonal antibodies to EPOR (B8) and by a set of short EPO-mimetic peptides (B9) (EMPs) that are unrelated in sequence to EPO and can be considered minimized hormones (B9) (B10) . The crystal structure of an agonist EMP1-EBP complex (B11) revealed a twofold symmetric dimer assembly (Fig. 1), whereas an antagonist peptide (EMP33) produces an asymmetric dimer that is apparently not permissive for JAK2 phosphorylation (B12) . These results, combined with the highly asymmetric EPO-EPObp structure (B13) , suggest that receptor dimer orientation affects EPOR activation.

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EBP, consisting of residues 1 to 225 of the human EPOR, was expressed and purified as described (B14) . The crystal structure of native, unliganded EBP was determined at 2.4 .A ring. resolution by molecular replacement (Table 1). Each EBP monomer (B15) consists of two FBN-III folds (D1 and D2), connected at an approximate right angle, as in other cytokine receptors (B16) . However, the native EBP unexpectedly forms a cross-shaped dimer (Fig. 1A). The self-dimer interface (B17) (Figs. 1 and 2A) involves an almost perfect twofold symmetric interaction of 24 residues from five of the six binding loops L1, L3, L4, L5, and L6 (B18) and a small loop segment (L5a) between strand C (prime) and E in D2 (Fig. 2B) that are markedly similar to those used to bind EPO (Fig. 2C). A hydrophobic core includes two layers, from four aromatics, Phe.sup(93) (L3), and Phe.sup(205) (L6) of each EBP that form a crownlike ring structure, reminiscent of the hydrophobic interface between EMP1 and EBP (B11) , and from Leu.sup(33) (L1), Pro.sup(149) (L5), and Met.sup(150) (L5). A large number of polar residues provide sufficient hydrogen bonding (B19) to fix the geometry of the quaternary association.

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00505223 (THIS IS THE FULLTEXT)
Structural Basis of Plasticity in **T Cell Receptor**
Recognition of a Self Peptide-MHC Antigen
Garcia, K. Christopher; Degano, Massimo; Pease, Larry R.; Huang, Mingdong; Peterson, Per A.; Teyton, Luc; Wilson, Ian A.
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Abstract: The **T cell receptor** (**TCR**) inherently has dual specificity. T cells must recognize self-antigens in the thymus during maturation and then discriminate between foreign pathogens in the periphery. A molecular basis for this cross-reactivity is elucidated by the crystal structure of the alloreactive 2C **TCR** bound to self peptide-major histocompatibility complex (pMHC) antigen H-2K.sup(b)-dEV8 refined against anisotropic 3.0 angstrom resolution x-ray data. The interface between peptide and **TCR** exhibits extremely poor shape complementarity, and the **TCR** (beta) chain complementarity-determining region 3 (CDR3) has minimal interaction with the dEV8 peptide. Large conformational changes in three of the **TCR** CDR loops are induced upon binding, providing a mechanism of structural

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plasticity to accommodate a variety of different peptide antigens. Extensive **TCR** interaction with the pMHC a helices suggests a generalized orientation that is mediated by the V.inf(a) domain of the **TCR** and rationalizes how **TCRs** can effectively "scan" different peptides bound within a large, low-affinity MHC structural framework for those that provide the slight additional kinetic stabilization required for signaling

Text: The phenomenon of MHC restriction is the basis of the cell-mediated immune response to foreign pathogens (B1) . The central molecular event governing this process is the engagement of the clonotypic a (beta) **TCR** by particular MHC class I or class II molecules in association with processed peptides (B2) . Upon engagement of the pMHC, a proliferative signal is transduced into the T cell by subsequent activation of the nonclonotypic members of the **TCR** signaling complex: CD8 (class I) or CD4 (class II), and CD3 (gamma) , (delta) , epsilon , and (zeta) (B3) (B4) .

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It has become clear that a structural plasticity, or flexibility, in recognition of pMHC (B5) (B6) and a biological plasticity in response to ligand (B3) (B4) (B7) (B8) (B9) are essential properties for the survival and function of T cells. Thymic development of T cells depends on weak interactions with self pMHC ligands (B10) . T cells selected for maturation then exhibit high frequencies of alloreactivity, or cross-reactivity, against both self and foreign pMHC complexes in the periphery (B11) . This **TCR** cross-reactivity can manifest itself in a range of different

biological outcomes, depending on the pMHC ligand (B5) (B6) (B7) (B8) , and includes agonist and antagonist effects (B8) , which have been correlated to the half-life of the **TCR**-pMHC complex and co-receptor association (B12) . An important question is whether there are structural properties unique to the **TCR**-pMHC interface that facilitate this broadened specificity.

T cell receptor structure determinations have illuminated similarities and differences with antibodies and how the **TCR** may be particularly suited to bind pMHC (B13) (B14) (B15) (B16) .

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The orientation of the **TCR** to the pMHC has been determined for two **TCR**-pMHC complexes (B15) (B16) , one of which represents a refined structure at 2.6 angstrom (B16) . The overall topology of these complexes could be reconciled with earlier predictions inferred from biological data (B17) (B18) (B19) .

We have focused our efforts on the murine 2C **TCR** system (B20) (B21) , which is the only a (beta) **TCR** for which distinct self (H-2K.sup(b)-dEV8) (B6) and foreign [H-2K.sup(bm3)-dEV8 (B6) and H-2L.sup(d)-p2Ca (B22)] ligands have been defined (B23) . Thymocytes of 2C transgenic mice are positively selected in the presence of H-2K.sup(b) and negatively selected in the presence of the allo-ligands H-2K.sup(bm3) (a naturally occurring, two-amino acid mutant of H-2K.sup(b)) or H-2L.sup(d) (B21) . dEV8 is a murine self-peptide, derived from intracellular processing of the murine mitochondrial respiratory protein complex (MLRQ), that was eluted from H-2K.sup(b)-and H-2K.sup(bm3)-bearing cells (B6) . When bound to H-2K.sup(b), dEV8 is a weak agonist for the 2C cytotoxic T cell but a strong agonist for the 2C allo-ligand H-2K.sup(bm3). Therefore,

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dEV8 may be one of a number of peptides bound to H-2K.sup(b) that is capable of selecting 2C thymocytes (B6) . A crystal structure of 2C in complex with H-2K.sup(b)-dEV8 can allow us to explain how just two amino acid changes are sufficient to convert H-2K.sup(b) into an alloreactive ligand (B21) .

We report here the refined crystal structure of the mouse 2C **TCR** in complex with mouse MHC class I H-2K.sup(b) bound to the self-peptide dEV8 (EQYKFYSV) (B24) . We also briefly describe the 2.3 angstrom structure of H-2K.sup(b)-dEV8, which, along with the unliganded 2.5 angstrom structure of the 2C **TCR** (B15) , allows us to assess whether there are structural alterations in either the **TCR** or pMHC upon complexation. We can now more clearly explain the degenerate specificity of **TCR**-pMHC interaction in terms of a structural plasticity in the **TCR**-pMHC interface. The ability to alter the shape of the **TCR** combining site through deformation of the peptide-contacting complementarity-determining region (CDR) loops and their side chain orientations, along with large unfilled spaces in the interface, permits

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useful accommodation of different ligands. This in turn gives rise to the biological and functional plasticity that is based on varying affinities

and stabilities observed in most **TCR** systems in the in vivo signal transduction events.

Overall structure. The 2C **TCR** and H-2K.sup(b)-dEV8 were expressed and purified from Drosophila melanogaster cells and cocrystallized (B23) . The structure was determined by molecular replacement and refined with the use of multidomain real-space averaging and torsion angle dynamics (B25) (Table 1). The diffraction of these crystals is markedly anisotropic along the b* direction, thus limiting the effective resolution of the refined structure (maximum resolution along a* and c* is beyond 3.0 angstrom , but only ~4.2 angstrom along b*). Despite the presence of this anisotropic decay, all of the domains of the two **TCR**-pMHC complexes in the asymmetric unit are ordered (B26) , with the highest quality electron density being in the **TCR**-pMHC interfaces. The relation of the two molecules in the asymmetric unit (B27) does not support other crystallographically derived dimerization models for

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TCR-pMHC complexes (B28) .

The overall relative orientations of the **TCR** and pMHC in the refined 2C-H-2K.sup(b)-dEV8 complex are identical to those derived from the original molecular replacement solution (B15) . The **TCR** crosses the pMHC in an approximate diagonal orientation, in which the **TCR** a chain lies over the bound peptide NH.inf(2)-terminal residues and the (beta) chain covers the peptide COOH-terminal residues (Figs. 1 and 2). Given the steric limitations that the MHC helices place on the depth of the approach of the **TCR** to the bound peptide, the diagonal orientation allows for the deepest docking solution of the **TCR** CDRs onto the pMHC surface. The unusual noncanonical fold of the **TCR** C.inf(a) domain (B15) is confirmed in each of the two complexes.

The **TCR**-pMHC interface. About 1876 angstrom .sup(2) of surface is buried in the 2C-K.sup(b) interface, of which 900 angstrom .sup(2) is contributed by the **TCR** and 976 angstrom .sup(2) by the pMHC (B25) . Within the pMHC composite surface, about 222 angstrom .sup(2), or 23% of the total, constitutes the bound dEV8 peptide, and 754 angstrom .sup(2)

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(77%) the buried surface from the MHC a helices. The small fraction of surface contributed by the peptide is a reflection of its deeply buried location within K.sup(b) molecules, which limits the amount of exposed surface area, as originally proposed in the H-2K.sup(b)-VSV and H-2K.sup(b)-SEV structures (B29) . In the A6-HLA-A2-Tax complex (B16) , the total buried surface area in the interface is similar (B30) , but the peptide fraction is greater (33%).

All of the 2C **TCR** CDRs contribute to the buried surface area in the interface (Fig. 1), contrary to the situation seen in the structure of the human A6 **TCR** in complex with HLA-A2-Tax (B30) , where (beta) chain CDRs 1 and 2 make essentially no contributions (B16) . For 2C, slightly more surface is buried by the a chain (470 angstrom .sup(2)) than the (beta) chain (430 angstrom .sup(2)), but within each chain the distribution of buried surface area by the CDRs varies: CDR1.inf(a), 214 angstrom .sup(2); CDR2.inf(a), 110 angstrom .sup(2); CDR3.inf(a), 140 angstrom .sup(2); CDR1.inf((beta)), 160 angstrom .sup(2); CDR2.inf((beta)), 167 angstrom .sup(2); CDR3.inf((beta)), 89 angstrom .sup(2);

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and HV4, 10 angstrom .sup(2). CDR3.inf((beta)) contributes the least buried surface of all the CDRs and is positioned over a largely empty pocket in the interface (Fig. 1). The overall contact surface is formed from 21 **TCR**, 16 MHC, and 5 peptide residues (Table 2).

TCR contacts with the MHC helices. Of the ~41 total intermolecular contacts between the **TCR** and pMHC, 27 are derived from CDR contacts with highly conserved MHC a1 and a2 a-helical residues (Table 2). CDRs 2.inf(a) and 2.inf((beta)) lie directly on top of the a2 and a1 helices, respectively, and, therefore, interact exclusively with the MHC (Fig. 2). CDRs 1.inf(a) and 1.inf((beta)) lie between the helices and are thus able to contact both peptide and MHC simultaneously. As originally speculated (B15) , the paucity of bulky side chains at the apices of CDRs 2 and 3 in both chains (Fig. 2A) allows the 2C **TCR** to approach the MHC heavy chain so as to maximize main chain van der Waals contacts and to position the two CDR3s to "read-out" the contents of the peptide binding groove. The predominant interaction of the **TCR** with the MHC helices in this complex, as also observed in the A6-HLA-A2-Tax complex (B16) ,

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provides structural confirmation of long-standing hypotheses that the **TCR** repertoire must have evolved primarily with reactivity toward conserved features of the MHC heavy chain so that the most diverse portions of the receptor can discriminate among antigenic peptides (B17) (B18) (B19A number of contacts (Table 2) at the periphery of the interface between the MHC helices and CDRs 1 and 2 appear to be between highly conserved residues and may play a key role in dictating (or steering) a generalized orientation. In particular, Ser.sup(27).sup(a) of CDR1.inf(a), which hydrogen bonds to the conserved K.sup(b) residue Glu.sup(58) (Fig. 3 A), and Ser.sup(51).sup(a) of CDR2.inf(a) [contacts Glu.sup(166) (Fig. 3A)] are the most frequently occurring residues to occur in V.inf(a) gene sequences at these positions (B31) . These interactions between conserved residues are consistent with recent data indicating a critical role for V.inf(a) residues 27.inf(a) and 51.inf(a) in the restriction of particular murine **TCRs** (V.inf(a)3.1 and V.inf(a)3.2) for MHC class I versus class II (B32) . In class II MHC molecules, the approximate corresponding residues of the class I H-2K.sup(b) Glu.sup(58) and Glu.sup(166) are different but

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still highly conserved (B33) . Other potentially conserved contacts appear between a (Tyr.sup(31).sup(a)) and (beta) (His.sup(29).sup((beta)), Glu.sup(56).sup((beta))) chain residues to the MHC helices (Table 2).

Overall, the V.inf(a) CDR1 and CDR2 contact residues appear to be more highly conserved not only within K.sup(b)-restricted **TCRs** but also across other **TCRs** compared with the corresponding (beta) chain contact residues. In the A6-HLA-A2-Tax crystal structure, the A6 **TCR** V.inf(a) has a similar overall orientation as V.inf(a) in our complex, but it has minimal contact between the (beta) chain CDRs 1 and 2 and the pMHC. These similarities and differences would strongly infer that it is the a chain that dictates the orientation of that complex (discussed below).

A conserved framework for **TCR** binding to the MHC helices, or a

generalized orientation, would enhance the flexibility in pMHC recognition by providing a scaffold in which the centrally located peptide can be finely sampled by the **TCR** (B18) . A large, conserved buried surface of relatively low affinity would facilitate short-lived complex formation

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by the **TCR** and MHC and subsequent "scanning" of the peptide (B34) .
A naturally occurring mutant of H-2K.sup(b), termed H-2K.sup(bm3) (Asp.sup(77) to Ser, Lys.sup(89) to Ala), is an alloreactive ligand for, and negatively selects, the 2C **TCR** (B21) . When bound to dEV8, H-2K.sup(bm3) generates a strong 2C cytotoxic T cell response (B6) . Of the two **mutations** in H-2K.sup(bm3), Asp.sup(77) to Ser has been identified as the one that causes the alloreactive response (B21) . In the 2C-H-2K.sup(b)-dEV8 structure, Asp.sup(77) lies underneath CDR2.inf((beta)) but does not contact 2C; instead, it forms a hydrogen bond to the main chain of the P8 peptide residue. Replacement of Asp.sup(77) with Ser could disrupt this peptide contact and potentially alter the position of the peptide residues in contact with the **TCR** (especially Ser.sup(P7)) and also the conformation of the COOH-terminal region of the a1 helix, which is in contact with CDR2.inf((beta)). Additionally, removal of the Asp.sup(77) negative charge would alter the electrostatics of this patch of pMHC surface, which is buried by the **TCR** (B35) . Hence, even though Asp.sup(77) is not in direct contact with the **TCR**, its removal would

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clearly cause structural and electrostatic changes perceptible to 2C and lead to an alloreactive response.
TCR contact with bound peptide. The dEV8 peptide (EQYKFYSV) (B24) runs from CDR1.inf(a) to CDR1.inf((beta)) diagonally across the **TCR** surface between CDRs 3.inf(a) and 3.inf((beta)) (Fig. 2B), which lie primarily within the peptide binding groove between the a helices (Fig. 2D). The **TCR** interaction with the peptide is mediated directly and indirectly by hydrogen bonds to the functional groups of the upward-facing side chains (P1, P4, P6, and P7) from CDRs 1.inf(a), 1.inf((beta)), 3.inf(a), and 3.inf((beta)), which are in simultaneous contact with the a1 and a2 helices of the MHC (Figs. 1 and 2). The large hydrophobic central cavity between CDRs 3.inf(a) and 3.inf((beta)) remains unfilled, contrary to our previous expectations (B15) ; CDR3.inf((beta)) appears to have only a very limited interaction with the peptide at residue Tyr.sup(P6) through a single contact with Gly.sup(97).sup((beta)) (Fig. 3B). Thus, CDR3.inf((beta)), which has been implicated in playing a primary role in peptide recognition in other **TCRs** (B16)

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Ref	Items	Index-term
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E2	1	AU=KRANZ, DAVID LORD
E3	17	*AU=KRANZ, DAVID M
E4	95	AU=KRANZ, DAVID M.
E5	1	AU=KRANZ, DAVID MICHAEL
E6	2	AU=KRANZ, DELPHINE
E7	19	AU=KRANZ, DIETER
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